

REVIEW

Two forms of reactive arthritis?

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Abstract

Inflammatory arthritides developing after a distant infection have so far been called reactive or postinfectious, quite often depending on the microbial trigger and/or HLA-B27 status of the patient. For clarity, it is proposed that they all should be called reactive arthritis, which, according to the trigger, occurs as an HLA-B27 associated or non-associated form. In addition to the causative agents and HLA-B27, these two categories are also distinguished by other characteristics. Most important, HLA-B27 associated arthritis may occur identical to the Reiter's syndrome with accompanying urethritis and/or conjunctivitis, whereas in the B27 non-associated form this has not been clearly described. Likewise, only the B27 associated form belongs to the group of spondyloarthropathies.

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Reactive arthritis was originally defined as a synovitis developing after a distant infection, and it was distinguished from postinfectious arthritis by absence of bacterial components in the joint tissue.^{1,2} The main effort of research in this field has been focused on the arthritides triggered by *Chlamydia*, *Yersinia*, *Salmonella*, *Shigella*, or *Campylobacter*, usually in HLA-B27 positive persons. However, several other infections may induce a similar reactive arthritis. These patients have only remained scattered, and a clear association of their disease to B27 is missing. Therefore, according to the triggering agent, the arthritides fulfilling the original definition of reactive arthritis could be considered to occur in two forms, one HLA-B27 associated and another HLA-B27 non-associated. Such a categorisation has already previously been considered,³⁻⁶ but certain confusion still prevails.

Aetiology

The majority, in some studies up to 90%, of the patients contracting reactive arthritis after an infection with *Chlamydia*, *Salmonella*, *Shigella* or *Yersinia* are HLA-B27 positive.^{7,8} The same applies to reactive arthritis following diarrhoea attributable to *Campylobacter jejuni* or to overgrowth of *Clostridium difficile*. Of the 19 B27 typed patients reported so far with reactive arthritis after *Clostridium difficile* associated diarrhoea 12 (63%) were B27 positive.⁹⁻¹³ It

must be emphasised that it is not known whether the arthritis is attributable directly to *Clostridium difficile* or to changes of the intestinal flora; bacterial structures have not been demonstrated in the synovial tissue as is the case in arthritis triggered by *Chlamydia*, *Salmonella*, *Shigella* or *Yersinia*.¹⁴⁻²¹ It should also be noted that both the capacity for arthritis induction as well as B27 association may greatly vary even within a single bacterial species. Good examples are *Yersiniae* and *Salmonellae*.^{22,23} In *Salmonella* outbreaks, a B27 frequency as low as 27% among the arthritis patients has been reported, which, however, is considerably more than in the general population.²³

Among the pathogens in the genus *Campylobacter*, *Campylobacter jejuni*, *fetus* and *lari* are known to cause reactive arthritis.^{24,25} *Chlamydia trachomatis* is a common cause of reactive arthritis, and cases attributable to *Chlamydia pneumoniae*²⁶⁻³⁰ and *Chlamydia psittaci*³¹ have also been reported. Among *Clostridia*, *Clostridium difficile* is the only one associated with reactive arthritis. Regarding salmonellas, no evidence exists to indicate that any of the species or serotypes that are human pathogens would be unable to induce reactive arthritis.³²⁻³⁴ *Shigella flexneri* has been thought to be the only one out of the four *Shigella* species capable of triggering reactive arthritis, but on the basis of two reports it seems that also the less virulent *Shigella sonnei* has this capacity.^{35,36} Within the genera of *Yersiniae*, both *Y enterocolitica* and *Y pseudotuberculosis* are causes of reactive arthritis, with arthritogenicity varying between and within different serotypes.^{1,22} A common nominator to all bacterial species discussed above is their capacity to trigger reactive arthritis predominantly in HLA-B27 positive persons.

Table 1 Bacterial genera with species triggering reactive arthritis

HLA-B27 association	
established	not established
<i>Campylobacter</i>	<i>Borrelia</i>
<i>Chlamydia</i>	<i>Brucella</i>
<i>Clostridium</i>	<i>Haemophilus</i>
<i>Salmonella</i>	<i>Hafnia</i>
<i>Shigella</i>	<i>Leptospira</i>
<i>Yersinia</i>	<i>Mycobacterium</i>
	<i>Neisseria</i>
	<i>Staphylococcus</i>
	<i>Streptococcus</i>
	<i>Ureaplasma</i>
	<i>Vibrio</i>

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Table 2 Laboratory characteristics in reactive and bacterial arthritis

Characteristics	Reactive arthritis	Bacterial arthritis
ESR mm 1st h (median)	79	78
CRP g/l (median)	129	125
Peripheral blood		
Leucocytes*10 ⁹ /l (median)	9.9	11.6
Synovial fluid (knee)		
Leucocytes*10 ⁹ /l (median)	19.0	36.0
Granulocytes; % of leukocytes (median)	85	89

These findings are based on a study of 20 patients with B27 associated reactive arthritis and of 20 patients with culture positive bacterial arthritis.⁶¹ Reactive arthritis was caused by *Yersinia* (14 patients), *Salmonella* (4) or *Chlamydia* (2).

Bacteria that have been reported to cause reactive arthritis in an HLA-B27 independent fashion are listed in table 1. Among these, the infections caused by *Borrelia burgdorferi* represent a special entity because of the highly variable nature of Lyme disease.³⁷⁻³⁹ From the members of the other bacterial genera in table 1, *Brucella abortus*, *Haemophilus influenzae*, *Hafnia alvei*, *Leptospirae*, *Mycobacteria*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Staphylococcus aureus*, *Streptococci*, *Ureaplasma urealyticum* and *Vibrio parahaemolyticus* have been reported to trigger a disease fulfilling the original definition of reactive arthritis.^{3-6 40-50} For none of these has an association to HLA-B27 been observed. Likewise, several viral, fungal and parasitic infections are known to induce reactive arthritis without any clear association to HLA-B27.^{6 51-55} The same applies to reactive arthritis accompanying inflammatory bowel diseases, intestinal bypass, acne, cystic fibrosis, etc.^{6 56-60} A feature shared by bacteria triggering B27 non-associated reactive arthritis is their capacity to cause bacterial (septic) arthritis. In fact, the clinical and laboratory diagnosis between reactive and bacterial arthritis is often extremely difficult or even impossible,^{42 61 62} (table 2), and knowledge of the bacteriological aetiology is of great help,⁶³ and Jalava *et al* (unpublished data).

Reactive or postinfectious?

A question remains whether an HLA-B27 non-associated arthritis after a known or unidentified infection elsewhere in the body should be called postinfectious or reactive. More than 20 years ago postinfectious arthritis

was defined as an inflammatory arthritis with non-culturable bacterial components present in the synovial tissue and reactive arthritis was regarded purely reactive, without any bacterial structures present at the site of synovial inflammation.^{1 2} Today it is known that non-viable bacterial structures are present in the synovial tissue of patients with B27 associated reactive arthritis^{14-21 65} as well as in other types of inflammatory arthritis.^{66 67} Likewise, bacterial DNA occurs in the synovial cells in postinfectious arthritis attributable to *Borrelia burgdorferi*,⁶⁸ *Chlamydia trachomatis*,⁶⁹⁻⁷² *Chlamydia pneumoniae*⁷³ or *Neisseria gonorrhoeae*,^{74 75} with bacterial cultures being negative. In other words, it has become impossible to distinguish postinfectious and reactive arthritis by these criteria. You are left only with the definition of a sterile arthritis after a distant infection; this may or may not include demonstration of non-culturable bacterial components at the site of inflammation.

You could argue that the definition of reactive arthritis should be restricted to the most typical causes—that is, to *Campylobacter*, *Chlamydia*, *Clostridium difficile*, *Salmonella*, *Shigella* and *Yersinia*, for which the HLA-B27 association is known, and all others should be called postinfectious. However, the actual aetiology of a clinically typical reactive arthritis may remain unknown. Therefore, restriction of the term reactive arthritis only to these bacterial triggers seems not justified. It could be logical to divide reactive arthritis into two forms, one HLA-B27 associated and another HLA-B27 non-associated. You should note that association or non-association to HLA-B27 is not 100%, and that so called B27 associated bacterial species may induce even chronic reactive arthritis in B27 negative subjects, indicating that presence of HLA-B27 is not a prerequisite for chronicity.⁷⁶ However, B27 most probably represents a risk factor for severity.⁷⁷

In addition to causative agents and HLA-B27, these two categories are distinguished by other characteristics (table 3). Most important, B27 associated arthritis may occur identical to the Reiter's syndrome with urethritis and/or conjunctivitis. In the B27 non-associated form

Table 3 Characteristics of the two forms of reactive arthritis

Characteristics	Reactive arthritis	
	HLA-B27 associated*	HLA-B27 non-associated†
Triggers	<i>Campylobacter</i> , <i>Chlamydia</i> , <i>Clostridium difficile</i> , <i>Salmonella</i> , <i>Shigella</i> , <i>Yersinia</i>	A variety of other microbes
Cultivable microbes present in joint	No	No
Microbial structures demonstrated in joint	Yes	So far only rarely
Differential diagnosis to bacterial arthritis	Mostly clear	Often unclear
Oligo- or polyarthritis	Usually oligoarthritis, most commonly in knee	Polyarthritis more common than in the B27 associated form; other joints than knee affected as well
Reiter's syndrome	Occurs	Not usual, but found after genitourinary infections§
Tendency for chronicity	Yes	Not clear
Evolution to ankylosing spondylitis	Possible	Not observed
Part of spondyloarthropathy group	Yes	No
Pathogenetic mechanisms	Similar to experimental antigen induced arthritis; in addition, an HLA-B27 associated mechanism	Similar to experimental antigen induced arthritis

*Sixty to ninety per cent of patients with this form of reactive arthritis are HLA-B27 positive.

†In patients with this form, HLA-B27 occurs in the same frequency as in the normal population.

§It is unclear if reactive arthritis developing after *Ureaplasma* and gonococcal infections is accompanied by other signs of Reiter's syndrome predominantly in HLA-B27 positive patients.

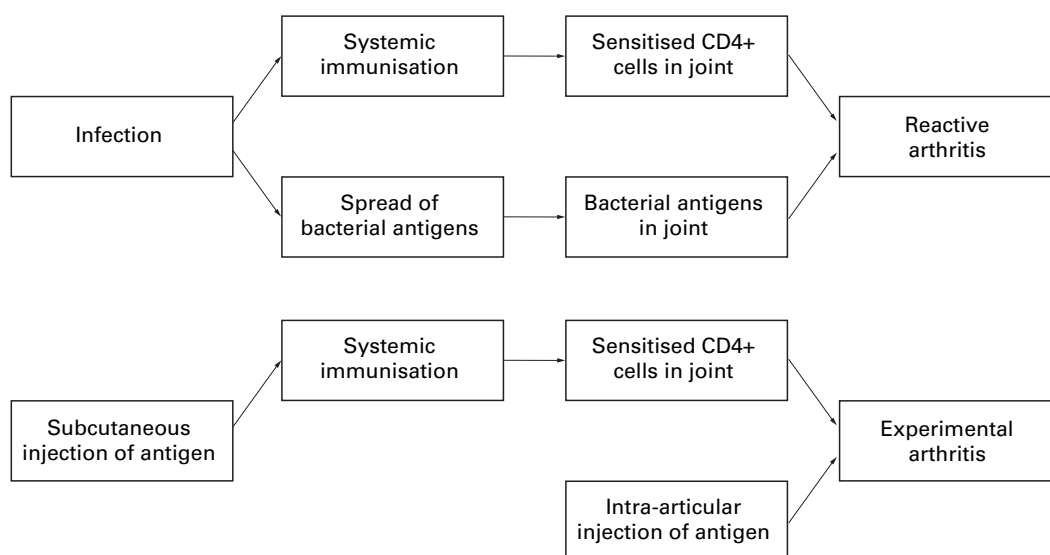


Figure 1 Pathogenesis of reactive arthritis, compared with that of experimental antigen induced arthritis. In the reactive arthritis, bacterial antigens end up in the joint tissue as a result of the infection. In the experimentally induced arthritis, the antigen (for example, BSA or non-viable bacterial antigen) is first given parenterally and two weeks later intra-articularly. In addition to the pathogenetic mechanism depicted here, an HLA-B27 dependent, so far unknown mechanism operates in the B27 associated form of reactive arthritis.

of reactive arthritis this has not been clearly described; it is unclear if reactive arthritis developing after *Ureaplasma* and gonococcal infections is accompanied by other signs of Reiter's syndrome predominantly in HLA-B27 positive patients.⁴⁷

Pathogenesis

Are living bacteria always required for induction of reactive arthritis? The answer seems to be no, because the disease has been reported after vaccination with killed *Salmonella* bacteria⁷⁸ or with recombinant hepatitis B viral protein.⁷⁹ In fact, human reactive arthritis greatly resembles experimental antigen induced arthritis, where an animal is first parenterally immunised and thereafter challenged intra-articularly with the same antigen (fig 1).⁸⁰⁻⁸¹ Arthritis then develops as a T cell mediated reaction at the site of the challenge, with an immune complex mediated mechanism potentially also contributing. In the human reactive arthritis, the patient has a preceding infection during which they become naturally immunised against the aetiological agent. You must assume that during that process—that is, usually in one to three weeks—microbial antigens are transported to the synovial tissue. This may occur intracellularly within mononuclear or other phagocytosing cells,⁸² as immune complexes⁵⁶⁻⁸³⁻⁸⁵ or even in the form of free antigen or proliferative bacterial bodies.⁶⁶⁻⁶⁷⁻⁷⁰ The consequence is a CD4+ cell mediated reaction, manifested as acute arthritis²¹⁻⁸⁶⁻⁹¹; immune complex mediated cytotoxicity may also participate,⁵⁶⁻⁸³⁻⁸⁵ similarly to experimental antigen induced arthritis. For development of a chronic antigen induced arthritis, a periodic or continuous supply of the antigen then is required. In the human patients this probably occurs from hidden reservoirs, which for instance for *Yersinia* seem to be the submucosal tissue.⁹²⁻⁹³

With this type of reasoning, the CD4+ cell mediated reaction, depending on immunologi-

cal presensitisation must be a crucially contributing factor in the early pathogenesis of B27 associated and non-associated forms of reactive arthritis. In addition, when the triggering agent in an HLA-B27 positive person is *Campylobacter*, *Chlamydia*, *Clostridium difficile*, *Salmonella*, *Shigella* or *Yersinia*, an HLA-B27 associated mechanism is involved. It is possible that this mechanism, with a CD8+ cytotoxicity probably involved,⁹⁴⁻⁹⁵ contributes to the chronicity and severity of arthritis in HLA-B27 positive persons.²¹⁻⁷⁷⁻⁹⁶⁻⁹⁷ You must note, however, that despite intensive research, the molecular basis of the B27 associated pathogenesis has so far remained a mystery.

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